CHEST Online Supplement

Sildenafil Preserves Exercise Capacity in Patients With Idiopathic Pulmonary Fibrosis and Right-sided Ventricular Dysfunction

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e-Appendix 1.

IRB Names and Approvals by Participating Site

Site Name	IRB name	Local STEP Protocol Number
University of California San Francisco	UCSF Committee on Human Research	H10449-30332-04
Emory University	Emory University IRB	IRB00002682
Mayo Clinic	Mayo Clinic Institutional Review Board	#07-006500
National Jewish	National Jewish Institutional Review Board	HS 2114
Tulane University	Tulane Human Research Protection Program	07-00234
University of California Los Angeles	University of California Los Angeles Office for Protection of Research Subjects	07-02-083-01
University of Chicago	Chicago Biomedicine IRB	15275A
University of Michigan	University of Michigan Medical School IRBMed	HUM00008613
University of Washington	University of Washington Office of Research Human Subjects	35397
Vanderbilt University	Vanderbilt University IRB	070724
Weill-Cornell	Weill Cornell Medical College IRB	0706009223
University of Alabama – Birmingham	University of Alabama at Birmingham IRB for Human Use	F070817001
Cleveland Clinic	Institutional Review Board of the Cleveland Clinic Foundation	#08-505
Duke University	Duke University Health System IRB	Pro00008253
Medical University of South Carolina	Medical University of South Carolina IRB	HR18474

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e-Appendix 2.

METHODS

Setting and Participants

The complete STEP-IPF protocol has been previously published.[1] See Web-only Supplement for full methods. This was a double-blind, placebo-controlled trial of sildenafil in advanced IPF subjects conducted at 14 IPFnet centers (see Acknowledgments). All subjects provided written informed consent. The study was approved by institutional review boards at participating institutions. Eligibility criteria included consensus criteria defined IPF and DLCO <35% predicted. Resting oxygen saturation <92% on 6L of supplemental oxygen, aortic stenosis, idiopathic hypertrophic subaortic stenosis or severe heart failure (left ventricular ejection fraction <25%) were additional exclusion criteria. Oral sildenafil (20 mg three times daily) was administered in a double-blind, randomized, placebo-controlled fashion. The study consisted of two periods. The first period was a 12-week double-blind, placebo-controlled study of sildenafil. The second period was a 12-week open-label extension. Results here are from the first period.

Outcomes and Follow-up

Key substudy outcome measures included 6MWD and QOL. The St. George's Respiratory Questionnaire (SGRQ), the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) and the EuroQol Group Dimension Self-Report Questionnaire evaluated QOL. SGRQ is scored from 0-100; higher scores indicate worse QOL[2]. Lower SF36 scores indicate worse QOL.[3] The EQ-5D rates QOL on a -0.59 to 1.00 scale self-report questionnaire and 0 to 100 on a visual-analogue scale; higher scores indicate better QOL.

For this separately funded substudy, echocardiograms were transferred to the University of Michigan for independent review (see Web-only Supplement for full echocardiogram protocol). All echocardiograms were performed prior to randomization and scored independently and in a blinded fashion by two cardiologists with advanced expertise in echocardiography. All subjects where baseline echocardiogram was available for central review were included in this substudy. Right ventricular hypertrophy (RVH) was graded as present or absent based on increased free-wall thickness (>5mm) or prominent and hypertrophied trabeculae. For these analyses, any level of abnormality in right ventricular systolic function was classified as dysfunction. As brain natriuretic peptide (BNP) has been suggested as a noninvasive marker for pulmonary hypertension in IPF,[4] BNP was also measured at enrollment.

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Cardiac Assessment

Right-sided cardiac structures were interrogated in multiple imaging planes, including parasternal short-axis, right ventricular inflow view, apical four-chamber and subcostal views; assessment of right-sided chamber sizes and function was based on integration of all available views. The following ten criteria were used in assessing structure and function: 1) Assessment of right atrial size was based on qualitative integration in multiple views and comparison to quantitative assessment of the left atrium and to other cardiac structures; and graded as normal, mild or moderate enlargement, or severe enlargement; 2) Right ventricular size assessment similarly was based on qualitative integration from multiple echocardiographic views and comparison to quantitative assessment of the left ventricle and to other cardiac structures; and graded as normal in size, mildly enlarged, moderately enlarged or severely enlarged; 3) Right ventricular hypertrophy was graded as present or absent based on increased free-wall thickness (> 5 mm) or prominent and hypertrophied trabeculae;. 4) Right ventricular systolic function was graded as normal, mildly decreased, moderately decreased or severely decreased based on integrated qualitative assessment in multiple imaging planes; 5) Tricuspid regurgitation severity was assessed using color-flow Doppler imaging in multiple planes, and graded using clinical criteria of absent, trace, mild, moderate or severe; 6) Tricuspid regurgitation peak velocity was assessed using continuous-wave spectral Doppler, and taken as the maximum value from all available views; 7) Right atrial pressure assessment was made by integrating right atrial size, tricuspid regurgitation severity and peak velocity, and distension and collapsibility of inferior vena cava; and taken as 5 mm Hg for normal right-sided chambers and without evidence of right ventricular hypertension or inferior vena cava dilation, 10 mm Hg in the setting of mild or moderate right atrial enlargement and/or evidence of up to moderate right ventricular hypertension, and 15 mm Hg in the setting of severe right atrial enlargement and evidence of at least moderate right ventricular hypertension and/or diminished collapsibility of inferior vena cava; 8) Right ventricular systolic pressure (mm Hg) was derived from tricuspid regurgitation peak velocity (VmaxTR) and right atrial pressure (RA) as: RVSP = (4 x VmaxTR2) + RA; 9) Left ventricular systolic function was defined as normal or reduced based on semiquantitative assessment. Where the measures differed between the two readers, an average of the two estimates was used.

Statistical Analysis

All analyses were performed using SAS 9.2 (Cary, NC). Baseline comparisons used Chi-square tests for categorical variables and Wilcoxon tests for continuous variables. Linear regression models estimated changes in outcome variables as functions of treatment group, cardiac parameters, and interactions between treatment group and cardiac parameters. A sensitivity analysis was conducted to determine if differences in the echo substudy population as compared to the entire population contributed to the differences in 6MWD change using inverse probability

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weighted (IPW) estimators. A logistic regression model (propensity score model) was constructed with the response variable of echo availability. The estimated propensity scores were used to construct weights which were applied to the standard linear regression models for change in 6MWD.

RESULTS

DLCO and Oxygen analyses

Models were also constructed to determine relationships between cardiac abnormalities, treatment and changes in DLCO% predicted and partial pressure of oxygen (PaO2) at 12 weeks. The parent STEP study demonstrated an improvement with sildenafil of 1.6 in DLCO% predicted (p=0.04). We conducted additional analyses to determine if these improvements are further modified by the presence of cardiac disease (e-Tables 3 and 4). A significant interaction between cardiac abnormality and treatment is seen with both RVH (p=0.02) and RVSD (p=0.01). Contrast tests indicate that for subjects with RVH and RVSD, an improvement in DLCO% predicted of 2.8 (p=0.02) and 2.1 (p=0.01) was seen in sildenafil versus placebo-treated subjects respectively. The parent STEP study also showed a small improvement in PaO2 with sildenafil, 3.0 mm Hg (p=0.02). As expected, contrast tests confirm that both subgroups with RVH and RVSD still demonstrate improvements in PaO2 with sildenafil treatment versus placebo, 8.2 mm Hg (p=0.04) and 13.5 mmHg (p=0.008) respectively. The interaction between RVH and sildenafil treatment is statistically significant (p=0.04) while the interaction between RVSD and sildenafil was not statistically significant (p=0.16). Hence the improvement in PaO2 experienced by those with RVH treated with sildenafil exceeds that for those without RVH.

References

1 Zisman DA, Schwarz M, Anstrom KJ, et al. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. N Engl J Med 2010; 363:620-628
2 Jones PW, Quirk FH, Baveystock CM. The St George's Respiratory Questionnaire. Respir Med 1991; 85 Suppl B:25-31; discussion 33-27
3 How to score version 2 of the SF-36(R) Health Survey. Lincoln, RI: QualityMetric, 2000
4 Leuchte HH, Neurohr C, Baumgartner R, et al. Brain natriuretic peptide and exercise capacity in lung fibrosis and pulmonary hypertension. Am J Respir Crit Care Med 2004; 170:360-365

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e-Table 1. HRCT and Pathology scoring for the Diagnosis of IPF between Treatment Groups

HRCT	Pathology	Sildenafil n=56	Placebo n=63	P-value
Definite IPF	Definite UIP	20/56 (35.7%)	15/63 (23.8%)	0.155
Definite IPF	Probable UIP	0/56 (0.0%)	5/63 (7.9%)	0.059
Definite IPF	Possible UIP	0/56 (0.0%)	1/63 (1.6%)	>0.999
Definite IPF	Probable NSIP	0/56 (0.0%)	1/63 (1.6%)	>0.999
Definite IPF	Possible NSIP	1/56 (1.8%)	0/63 (0.0%)	0.471
Definite IPF	Unavailable	25/56 (44.6%)	31/63 (49.2%)	0.619
Consistent with IPF	Definite UIP	7/56 (12.5%)	6/63 (9.5%)	0.603
Consistent with IPF	Probable UIP	2/56 (3.6%)	4/63 (6.3%)	0.683
Consistent with IPF	Possible UIP	0/56 (0.0%)	0/63 (0.0%)	NA
Consistent with IPF	Unavailable	1/56 (1.8%)	0/63 (0.0%)	0.471

e-Table 2. Demographic data by treatment status

	Sildenafil n=56	Placebo n=63	P-value
Age	68.7	66.9	0.40
FVC% predicted	57%	56%	0.67
DL_{CO}% predicted	26%	27%	0.42
Smoking Status			
Current	0/56 (0%)	0/63 (0%)	0.61
Past	44/56 (79%)	47/63 (75%)	
Never	12/56 (21%)	16/63 (25%)	
Duration of IPF (yrs)	1.67	1.67	0.66
Partial pressure of oxygen (mmHg)	66.1	70.8	0.10
Partial pressure of carbon dioxide (mmHg)	39.2	38.1	0.31
Arterial-alveolar gradient	29.6	27.5	0.33
6-minute walk distance (m)	255	290	0.06

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eTable 3. Mortality by Cardiac, right ventricular hypertrophy (RVH) and right ventricular systolic dysfunction (RVSD), and Treatment Status

	No RVH		RVH	
	Sildenafil	Placebo	Sildenafil	Placebo
12 week Mortality	2/46 (4.3%)	2/56 (3.6%)	0/9 (0.0%)	1/6 (16.7%)
95% CI	1.1%, 16.3%	0.9%, 13.5%	0.0%, 0.0%	2.5%, 72.7%
	No RVSD		**RVSD**	
	Sildenafil	Placebo	Sildenafil	Placebo
12 week Mortality	2/45 (4.5%)	2/51 (3.9%)	0/11 (0.0%)	1/11 (9.1%)
95% CI	1.1%, 16.8%	1.0%, 14.8%	0.0%, 0.0%	1.3%, 49.2%

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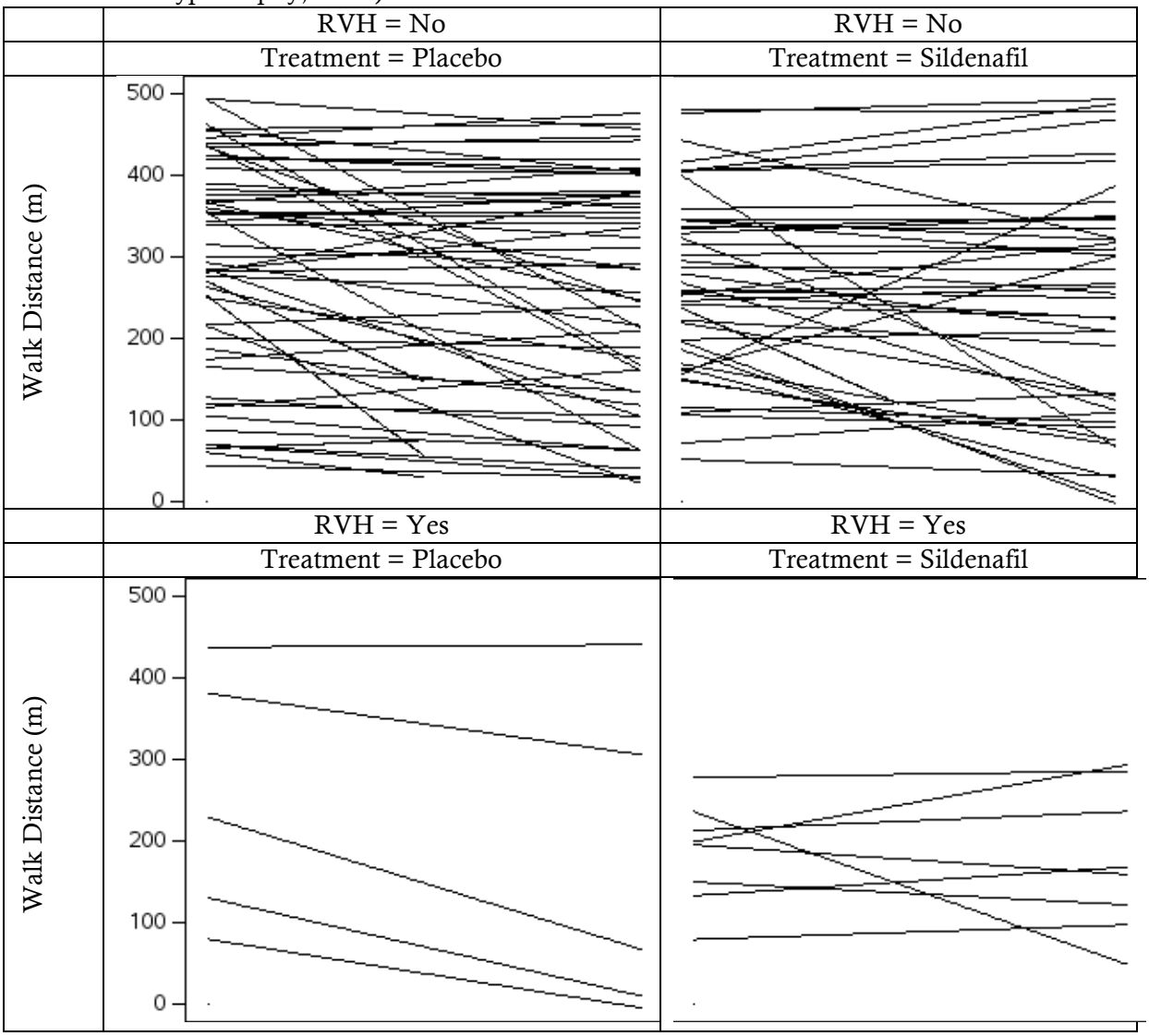
eFigure 1. Spaghetti plots demonstrating 12 week change in six minute walk distance by cardiac status (Right Ventricular Hypertrophy, RVH) and treatment.



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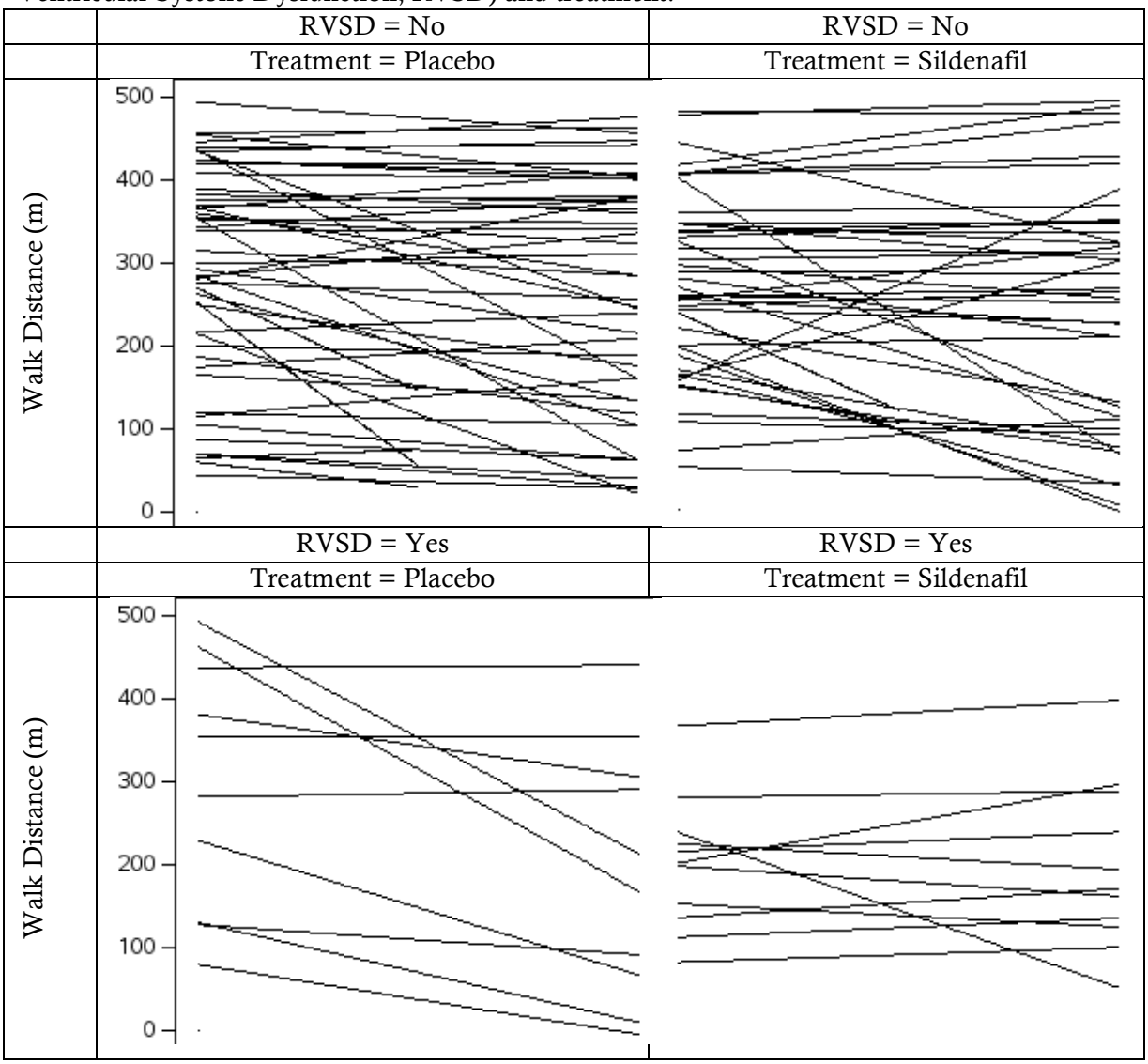
eFigure 2. Spaghetti plots demonstrating 12 week change in six minute walk distance by cardiac status (Right Ventricular Systolic Dysfunction, RVSD) and treatment.



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